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13. ABSTRACT (Maximum 200 words)

We demonstrate that the scaling properties of intracranial pressure (ICP) fluctuations and fluctuations of blood flow velocity in middle cerebral arteries are characterized by two scaling exponents. The short-time scaling exponent (STSE) determines the statistical properties of fluctuations in short-time intervals while the Hurst exponent describes the long-term fractal properties. Thus, the scaling properties of cerebral hemodynamics are reminiscent of those of arterial blood pressure (ABP). Specifically, in physiological conditions the mean value of arterial and cerebral short-time scaling exponents coincide. However, in patients with severe brain injuries the integrity of cerebral autoregulation may be compromised which leads to statistically significant discrepancy between the mean values of ABP and ICP scaling exponents. To shed new light on cerebral hemodynamics we employ a complex continuous wavelet transform to determine the instantaneous phase difference between ABP and ICP waveforms. For moderately elevated intracranial pressure the phase difference slowly evolves in time. However, high intracranial pressure may lead to synchronization of arterial and intracranial pressure signals. Such pathological synchronization may persist even for several hundreds cardiac beats. We use Shannon entropy to quantify the stability of ABP-ICP phase difference and discuss the applicability of such measure for assessment of cerebral autoregulation integrity.

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Introduction

The statistical properties of physiological fluctuations, such as found in the time series for heartbeat dynamics (1), respiration (2) , human locomotion (3; 4) and posture control (5), have been the focus of interdisciplinary research for more than two decades (6) . The rationale for this persistent interest has been twofold: to better understand complex self-regulatory control systems that produce such fluctuations (7) and to describe their dynamics with tools capable of capturing their nonlinear and/or non-stationary character (7). One outcome of this research has been a profound change in our understanding of the significance of homeostasis. Homeostasis – an organism's tendency to maintain approximately constant values of vital biological parameters, such as heart rate or blood pressure, has been the cornerstone of modern physiology since the turn of the twentieth century. However, the discovery of fractal and multifractal properties in physiological time series has lead to the conclusion that the intrinsic variability of many physiological phenomena reflects the adaptability of the underlying motorcontrol systems (8; 9).

This change of paradigm, associated with how we view the dynamics of physiologic phenomena, has not, to date, significantly influenced the studies of fluctuations in cerebral hemodynamics. In particular, the interpretation of the fluctuations in either intracranial pressure (ICP) or blood flow velocity in major arteries, remains unaltered. The slow adoption of ideas implemented earlier, for example, in cardiac dynamics, is to some extent surprising, taking into account that ICP monitoring has long been the fundamental component of critical care management of patients with severe brain injury. Moreover, transcranial Doppler ultrasonography (TCD), which allows physicians to *noninvasively* study cerebral blood flow velocities, is by now routinely employed in clinical practice.

A healthy human brain is perfused with blood flowing laminarly through cerebral vessels, providing brain tissue with substrates such as oxygen and glucose. It turns out that cerebral blood flow (CBF) is relatively stable with typical values between 45 and 65 ml/100g of brain tissue per second, despite variations in systemic pressure as large as 100 Torr. This phenomenon is known as *cerebral auto-regulation* and has been thoroughly documented not only in humans, but also in animals (10). Auto-regulation, which is mainly associated with changes in cerebrovascular resistance (CVR) of small precapillary brain arteries, is only one of at least four major mechanisms that regulate CBF. A considerable body of evidence suggests that CBF is influenced by local cerebral metabolic activity. As metabolic activity increases so does flow and vice versa (11). The actual coupling mechanism underlying this *metabolic regulation* is unknown, but most likely it involves certain vasoactive compounds such as adenosine, potassium, prostaglandins (11; 12), which are locally produced in response to metabolic activity. External *chemical regulation* is predominantly associated with the strong influence of CO_2 on cerebral vessels (13; 14). An increase in carbon dioxide arterial content leads to vasolidation, which in turn boosts CBF, while a decrease in CO_2 produces mild vasoconstriction and slows down CBF. The impact of the sympathetic nervous system on CBF is often ignored but intense sympathetic activity results in vasoconstriction . This type of neurogenic regulation can also indirectly affect cerebral flow via its influence on auto-regulation. The complex CBF regulation mechanisms are influenced, or even fundamentally altered, in many pathological states. However, the research interest has so far been predominantly focused on auto-regulation. This emphasis is justified since the human brain is

very susceptible to even short periods of ischemia. Thus, CBF must be maintained to ensure constant delivery of oxygen and glucose, as well as, the removal of metabolites.

The cerebral perfusion pressure (CPP) is the pressure gradient that drives CBF. CPP is defined as the difference between the arterial blood pressure (ABP) and the intracranial pressure (ICP). The breakdown of auto-regulation makes the brain vulnerable to changes in blood pressure. A far more dangerous disruption of CBF is associated with cerebral edema following trauma or major intracranial disease. This is because the skull is essentially a closed, bony box with constant volume filled with brain tissue, blood and cerebrospinal fluid. Since all three components are incompressible, if the brain enlarges, some blood and/or cerebrospinal fluid must be forced out of the skull, to prevent an increase in ICP. However, when the pathological swelling progresses this compensatory fluid-loss mechanism is eventually exhausted, and the ICP rapidly rises. This rise in pressure leads to a reduction of perfusion pressure to the point at which CBF falls below the ischemic threshold. To prevent neuronal death (secondary brain injury) CPP must be maintained by lowering the intracranial pressure and/or boosting mean arterial pressure. It is apparent that the simultaneous measurement of the ICP and ABP is the basis of brain injury management.

The fundamental problem is to determine the best measure of auto-regulation integrity. In two-point static methods one measures mean blood flow velocity in cerebral arteries before and after the *sustained* stimulus generated by blood pressure changes, elevated concentration of carbon dioxide or application of Acetazolamide (15-18). Due to advances in TCD it is now feasible to monitor the evolution of cerebral blood velocity , triggered by *transient* arterial pressure changes. The analysis of such evolution constitutes the foundation of so-called dynamical methods. For example, in the classical approach of Aaslid et al. (19) a step-wise drop in arterial blood pressure of about 20 Torr can be induced by rapidly deflating thigh blood pressure cuffs that have been inflated above the systolic pressure for approximately 2 min. After the cuffs' deflation ABP remains low for about 10 seconds, then returns gradually to its original level. Under physiological conditions, blood flow velocity in the middle cerebral artery (MCA) measured with TCD, initially decreases simultaneously with ABP by about 20%. However, after about one second auto-regulatory mechanisms become active and initial mean flow velocity is restored within 5 seconds. The relationship between cerebral blood flow velocity changes induced by arterial blood pressure manipulations has been studied most frequently using either a differential equation approach (20; 21) or a transfer function analysis. Employing a second order linear differential equation model of response to a rapid blood pressure drop, Ticks et al. (22) graded the response time of auto-regulation system using the ARI index. ARI varies between 0 (absence of auto-regulation) and 9 (very fast response). Transfer function analysis (23-25) sheds light on dynamical properties of cerebral auto-regulation from a different perspective. Within this framework, cerebral auto-regulation is considered a high-pass filter which transmits rapid changes in blood pressure, but dampens and delays low-frequency perturbations. Variations of blood pressure are the filter's input and cerebral velocities are its output. More specifically, this type of physiological filtering is quantified for a given frequency as a phase shift between the real and imaginary part of the complex transfer function. A phase shift that is close to zero, at frequencies which are usually dampened, are interpreted as a loss of cerebral auto-regulation. The application of dynamical methods has enabled the elucidation of the impairment of cerebral auto-regulation associated with carotid artery stenosis (26) and traumatic head injury (27).

It is worth pointing out some limitations of the existing dynamical methods. In about 20% of the cases studied, deflation of thigh cuffs does not produce a sufficient fall in blood pressure. In patients with critical cerebrovascular hemodynamics, such as premature newborns and

individuals suffering from heart or autonomic failure, blood pressure drops may be hazardous. Consequently, the search for auto-regulation tests which do not involve manipulations of ABP are the focus of the present research .

Material and methods

Experimental procedures

For 20 healthy subjects beat to beat finger arterial blood pressure was noninvasively recorded for at least 45 minutes (Finapres, Ohmeda). Subjects remained in a supine positions with their heads slightly elevated. MCA blood flow velocity (MCAfv) were measured in another group of 20 healthy volunteers without cerebrovascular risk factors using the Multidop T DWL Elektronische Systeme ultrasonograph. The 2-MHz Doppler probes were placed over the temporal windows and fixed at a constant angle and position. The measurements were taken continuously for at least two hours in the subjects at supine rest. The long-term ICP monitoring of 15 patients with traumatic brain injuries was done with either a ventricular catheter or parenchymal fiber-optic pressure transducer. The data acquisition setup is described in Appendix I.

Determination of scaling properties

Detrended Fluctuations Analysis (see (28) and references therein) is commonly used to determine scaling properties of physiological time series. Its main drawback is associated with strong susceptibility to periodic trends. Periodic components are prevalent in hemodynamics of patients with severe injuries (29) and consequently it is necessary to employ method free of this deficiency.

Let us consider the wavelet transform of self-affine function $y(t)$:

$$W[y](a,t_0) = \frac{1}{\sqrt{a}} \int_{-\infty}^{\infty} y(t)\psi^*_{a;t_0} dt, \qquad [1]$$

where

$$\psi_{a;t_0} = \psi\left(\frac{t-t_0}{a}\right) \qquad [2]$$

and $\psi(t)$ is the analyzing wavelet (mother function). If y (t) is the self-affine function then $y(ct)/c^H$ has the same statistical properties:

$$y(t) \cong y(ct)/c^H . \qquad [3]$$

Inserting [3] in to [1] we obtain:

$$W[y](ca, ct_0) \cong c^{1/2+H} W[y](a, t_0). \qquad [4]$$

Averaging with respect to translation parameter t_0 :

$$W[y](a) = < W[y](a, t_0) >_{t_0} \qquad [5]$$

leads to the expression which may be readily employed to determine the scaling exponent H :

$$W[y](ca) = c^{1/2+H} W[y](a).\qquad\qquad [6]$$

Specifically, one determines $1/2 + H$ as a slope of linear fit to $W[y](a)$ as a function of a in double logarithmic plot. This approach to determination of scaling exponents is known as Average Wavelet Coefficient (AWC) method (30).

Phase synchronization

Let us consider two signals $s_1(t)$ and $s_2(t)$ and their corresponding instantaneous phases ϕ_1 and ϕ_2. The phase synchronization takes place when:

$$n_1\phi_1 - m\phi_2 = const,\qquad\qquad [7]$$

where *n, m* are integers indicating the ratios of possible frequency locking. Herein we consider only the simplest case $n = m = 1$. Furthermore, as with most biological signals contaminated by noise we are forced to search for approximate phase synchrony, i.e.

$$\phi_1(t) - \phi_2(t) \approx const.\qquad\qquad [8]$$

Thus, the studies of synchronization involve not only the determination of instantaneous phases of signals but also introduction of some statistical measure of phase locking (31).

The instantaneous phase $\phi(t_0)$ of a signal s can be readily extracted by calculating wavelet transform with complex mother function (cf. [1]):

$$\exp[i\phi(t_0)] = W[s](a,t_0) / |W[s](a,t_0)|.\quad [9]$$

We characterize the stability of phase difference $\Delta\phi = \phi_1 - \phi_2$ with the help of the index γ:

$$\gamma = (H_{max} - H)/H_{max}\qquad\qquad [10]$$

derived from the Shannon entropy:

$$H = \sum_{k=1}^{N} p_k \ln p_k.\qquad\qquad [11]$$

In the above formula N is the number of bins, p_k is the relative frequency of finding the phase difference within the *k*-th bin. Due to normalization in [10], $0 \leq \gamma \leq 1$. $\gamma=0$ corresponds to uniform distribution of phase differences (no synchronization) while $\gamma=1$ to perfect synchronization.

Results and discussion

Fig. 1 shows the DFA analysis of arterial blood pressure fluctuations of a healthy subject. It is apparent that the scaling properties are characterized by two exponents. The short-time scaling exponent (STSE) determines the statistical properties of fluctuations in short-time intervals while the Hurst exponent describes the long-term fractal properties. In Fig. 2 we present the example of fractal analysis of MCA blood flow velocity time series. The comparison of Fig. 1 and Fig. 2 suggests that the statistical properties of arterial pressure and cerebral fluctuations are similar. Specifically, the mean value of arterial short-time exponent $STSE_{ABP}=1.37 \pm 0.13$ and the mean value of the cerebral exponent $STSE_{TCD}=1.35 \pm 0.12$ are not statistically different as indicated by the corresponding boxplot (Fig. 3) and the outcome of Welch's variant of t-test (p=0.44). It turns out that in physiological conditions intracranial pressure time series exhibits similar statistical properties (Fig. 4). However, in patients with traumatic brain injuries (TBI) the nature of autoregulation may profoundly changes. Fig. 6 show four ICP waveforms of a TBI patient who underwent the active control of perfusion pressure. For each waveform we selected three segments (marked A, B or C) and calculated the values of the mean intracranial pressure, mean pressure at the percussion peak ICP_P and the short-time index $STSE_{ICP}$. The analysis of data data collected in Table I might strongly indicate the influence of elevated intracranial pressure on the value of $STSE_{ICP}$. In particular, STSE seems to decrease with growing ICP. However, in Fig. 6 we present autocorrelation function and mutual information for arterial and intracranial pressure time series. The strong oscillations of both autocorrelation and mutual information indicates the presence of strong pathological periodic component which may render the DFA calculations inaccurate. Fig. 7 gives example of AWC calculations for arterial blood pressure fluctuations (a) and intracranial pressure fluctuations (b). It is apparent that the influence of low-frequency pathological oscillations is limited to narrow interval indicated by the arrows. In Fig. 8 we point out to another difficulty associated with the application of DFA. The maximal value of the STSE which may be reliably determined depends on the order of the polynomial used to eliminate local trends. We generated two-scale Mandelbrot functions with values of STSE varying from 1.5 to 3.5 and fixed value of the Hurst exponent. Then, we estimated the value of STSE using DFA (first and second order) and AWC. The advantage of AWC over DFA is obvious (the correct estimates should fall in this figure along the diagonal). We performed the AWC calculations using 30 ABP and ICP waveforms obtained from 15 different patients and we found that the average value of $STSE_{ABP}^{AWC}$ to be equal to 1.56 ± 0.53 and the average value of $STSE_{ICP}^{AWC}$ to be equal 1.99 ± 0.45. Thus, in traumatic brain injury the values of the short-time scaling exponents no longer coincide. To verify whether the observed affect is directly related to changes in cerebral autoregulation integrity we performed the preliminary studies of phase synchronization between ABP and ICP time series. It turns out that for moderately elevated intracranial pressure the phase difference *slowly* evolves in time (Fig. 9). However, high intracranial pressure may lead to synchronization of arterial and intracranial pressure signals. Such pathological synchronization may persist even for several hundreds cardiac beats (Fig. 10) and is reflected by the vary high value of the corresponding Shannon entropy. The detailed data analysis is presented in two papers which are the results of this research project. Further studies should closely examine the relationship between the clinical information furnished by the scaling exponents and that provided by the phase synchronization analysis. We gratefully acknowledge the financial support of the ARO which made this research possible.

PUBLICATIONS SUPPORTED UNDER THIS GRANT

Scaling properties of cerebral hemodynamics

IVth International Symposium: Fractals in Biology and Medicine , Ascona, Switzerland, March 9-13, 2004 (to be published in conference proceedings)
Miroslaw Latka, Bartosz Telenczuk, Braham Goldstein, Waldemar Kolodziej, Dariusz Latka, and Bruce. J. West

Wavelet analysis of intracranial pressure time series

to be submitted to Physical Review E

Miroslaw Latka, Bartosz Telenczuk, Braham Goldstein, Waldemar Kolodziej, Dariusz Latka, and Bruce. J. West

Phase synchronization in cerebral hemodynamics

to be submitted to Physical Review

Miroslaw Latka, Bartosz Telenczuk, Dariusz Latka, Waldemar Kolodziej, Braham Goldstein, and Bruce. J. West

ADVANCED DEGREES EARNED DURING THE FUNDING PERIOD

- Bartosz Telenczuk: Dynamics of Cerebral Blood Flow.   M.Sc.
- Grzegorz Tomczyk: Dynamics of Intracranial Pressure.   M.Sc.

Figures
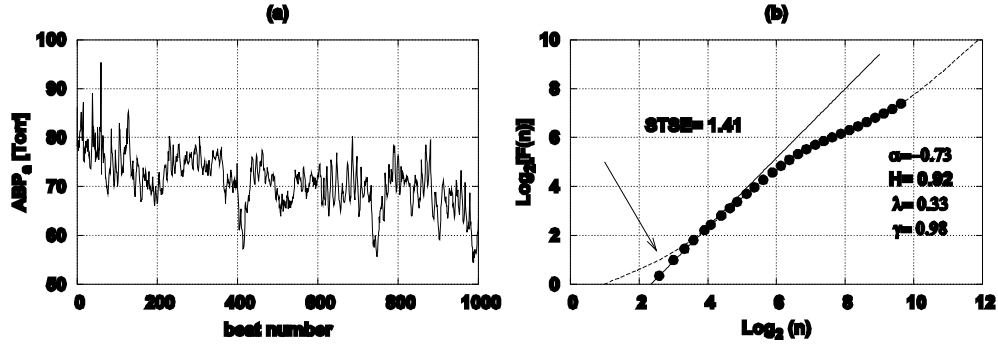
Fig. 1 (a) Time series of arterial blood pressure (averaged over a cardiac beat) of a healthy subject. First 1000 values of the time series are shown. (b) Detrended fluctuation analysis (DFA) of the time series shown in (a).
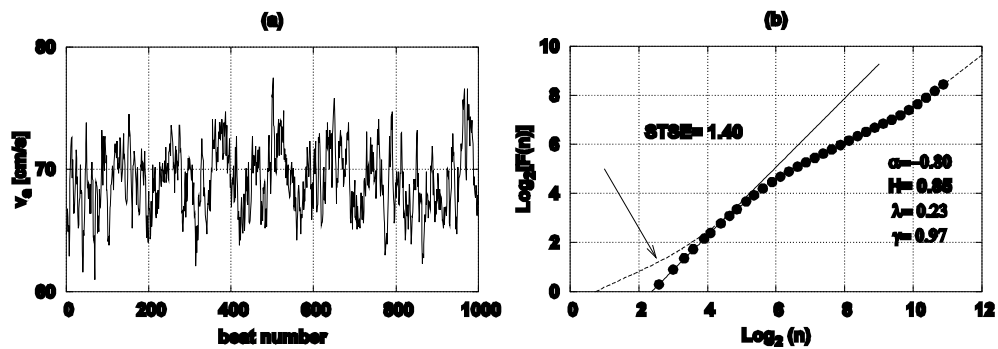

Fig. 2 (a) MCA flow velocity (averaged over a cardiac beat) time series for a healthy subject. First 1000 values of the time series are shown. (b) Detrended fluctuation analysis of the time series shown in (a).
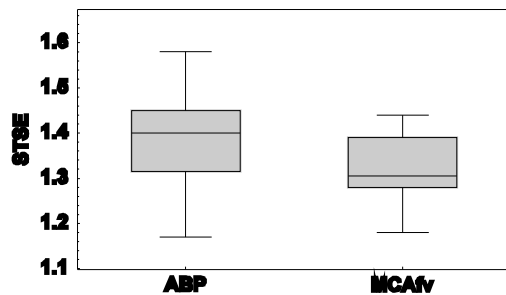

Fig . 3 Side-by-side boxplot for the values of the short-time scaling exponent (STSE) of fluctuations of arterial blood pressure (measured noninvaisively with Finapres) and fluctuations of MCA blood flow velocities (measured noninvaisively with TCD). It is apparent that the differences are not statistically significant.
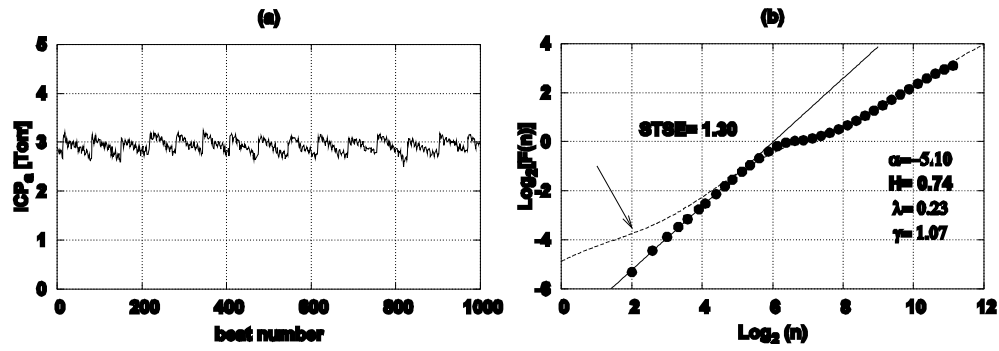
Fig. 4 (a) Time series of intracranial pressure (averaged over a cardiac beat) of a patient with traumatic brain injury. First 1000 values of the time series are shown. Intracranial pressure remained at level during measurement. (b) Detrended fluctuation analysis of the time series shown in (a).
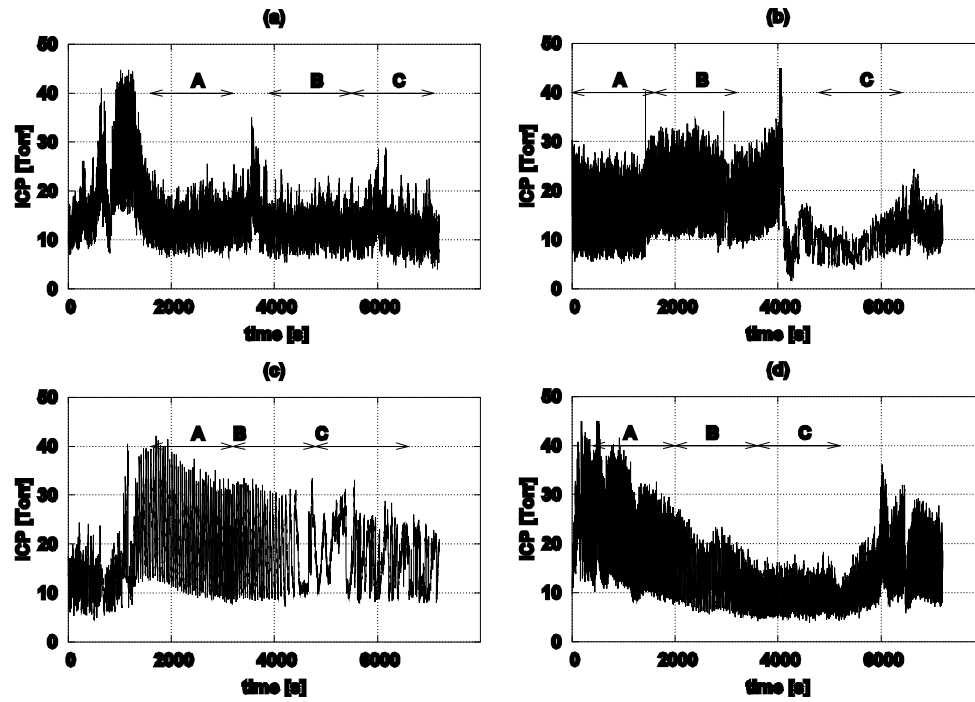

Fig. 5. (a)-(d) Time evolution of intracranial pressure obtained during long-term monitoring of a patient with traumatic brain injuries. The values of the STSE for the segments marked A, B, C in each figure are given in Table I.
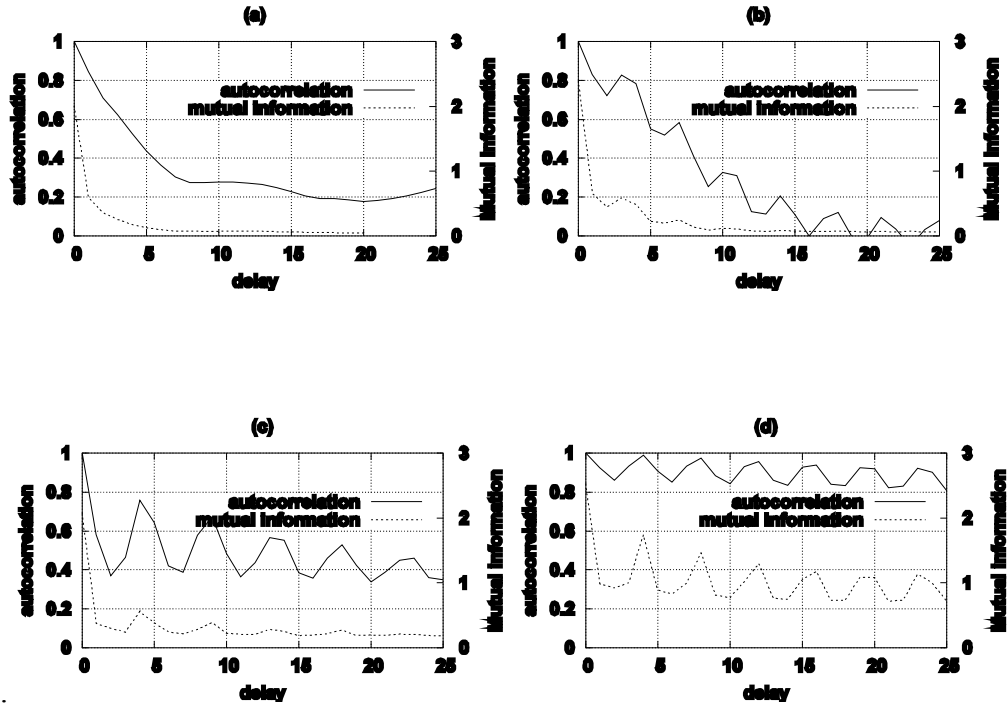
Fig. 6. Autocorrelation function and mutual information for: (a) arterial blood pressure time series, (b) ICP time series (physiological value of mean intracranial pressure), (c) and (d) ICP time series (high value of mean intracranial pressure associated with traumatic brain injury).
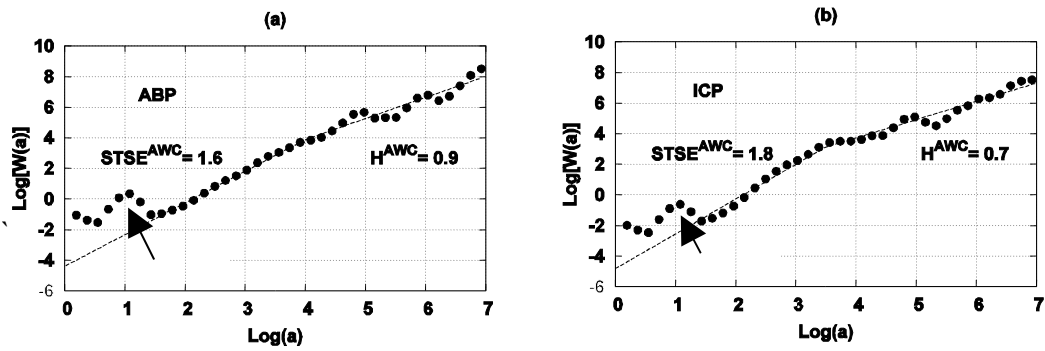

Fig. 7. Average wavelet coefficient (AWC) analysis of (a) arterial blood pressure fluctuations, (b) intracranial pressure fluctuations. The influence of low-frequency pathological oscillations is limited to narrow interval indicated by the arrows.
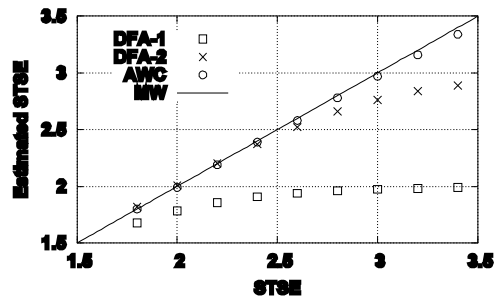
Fig. 8. Comparison of the accuracy of determination of STSE for two-scale Mandelbrot function. Circles correspond to AWC (Morlet wavelet). Boxes and crosses to first order DFA and second order DFA, respectively. Accurate estimates should fall along the diagonal.
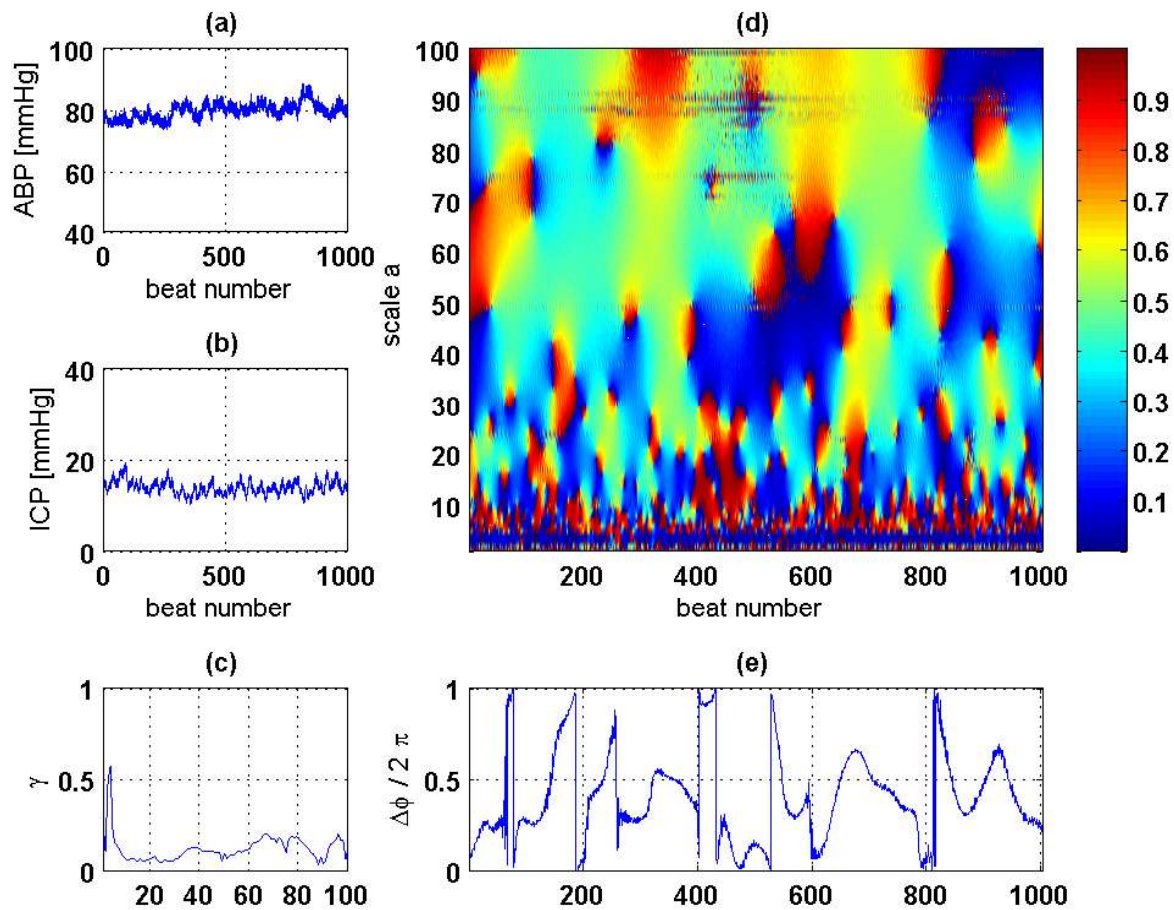

Fig. 9. Analysis of phase synchronization between fluctuations of (a) arterial blood pressure and (b) intracranial pressure. Figure (c) shows the value of strength of synchronization γ as a function of scale a, contour map (d) displays normalized phase difference, (e) is the plot of normalized phase difference for a=30. Week synchronization suggests adequate cerebral autoregulation.
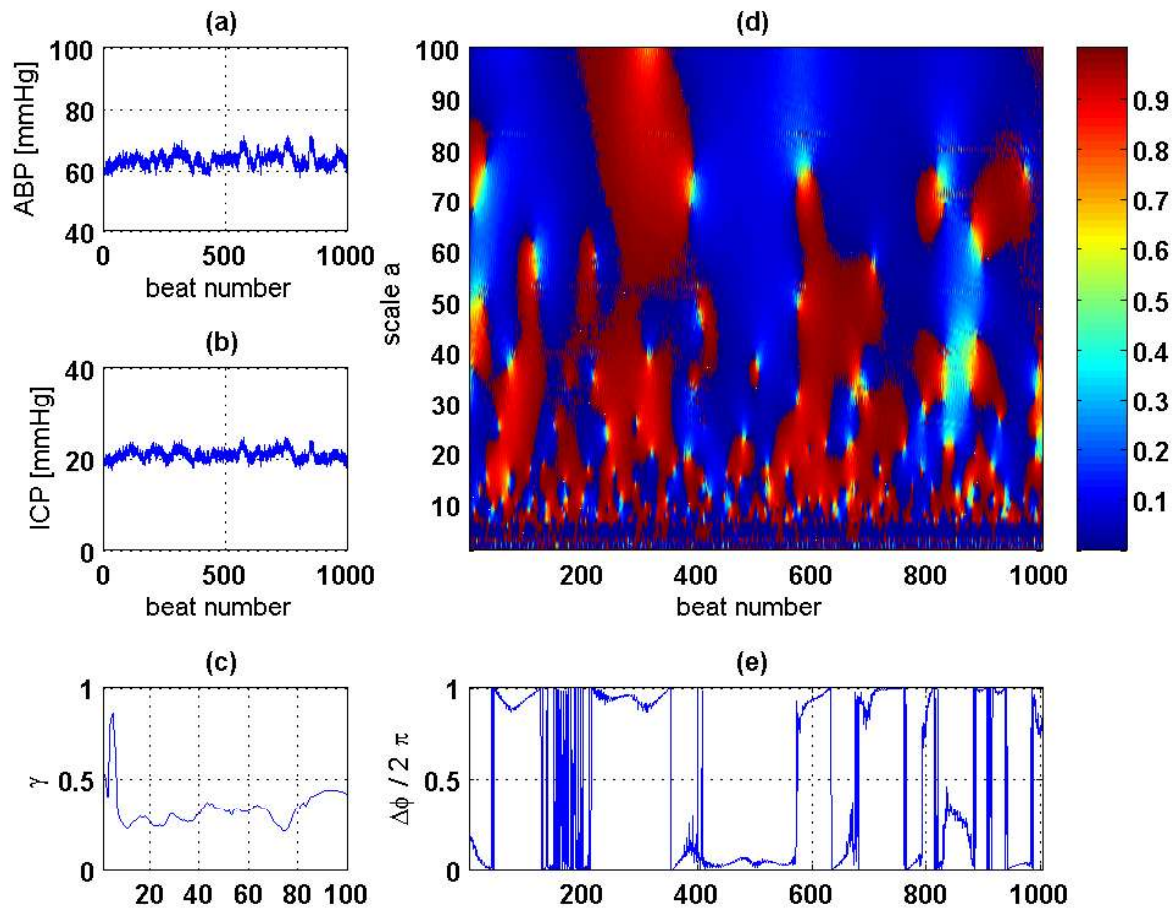
Fig. 9. Analysis of phase synchronization between fluctuations of (a) arterial blood pressure and (b) intracranial pressure. Figure (c) shows the value of strength of synchronization γ as a function of scale a, contour map (d) displays normalized phase difference, (e) is the plot of normalized phase difference for a=30. Strong synchronization indicates the failure of cerebral autoregulation.

Tables

| N	ICP			ICP_P			$STSE_{ICP}$		
	A	B	C	A	B	C	A	B	C
1	13.9	13.0	13.0	18.2	16.9	17.7	1.3	1.3	1.3
2	16.4	19.8	9.2	26.6	30.1	12.3	0.5	0.6	1.2
3	21.1	18.8	17.8	35.2	30.8	26.9	0.4	0.6	1.0
4	20.8	13.5	19.2	33.7	20.4	14.3	1.0	1.1	1.5

Table I. The values of short-time scaling exponent for the time series recorded during the long-term monitoring of a patient with traumatic brain injury (cf. Fig. 5). For each segment the mean value of ICP and the mean value of intracranial pressure at the percussion peak ICP_P is also given.

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Appendix I. Data acquisition setup.
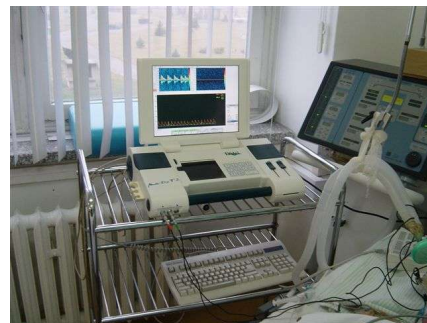
ICP transducer is connected to the patient monitor via the Codman ICP Express digital intracranial monitor. The measurement of blood flow velocity in selected cerebral artery is performed simultaneously with ICP, ABP, and ECG monitoring. The National Instruments measuring board is used to store analog signals on a PC.
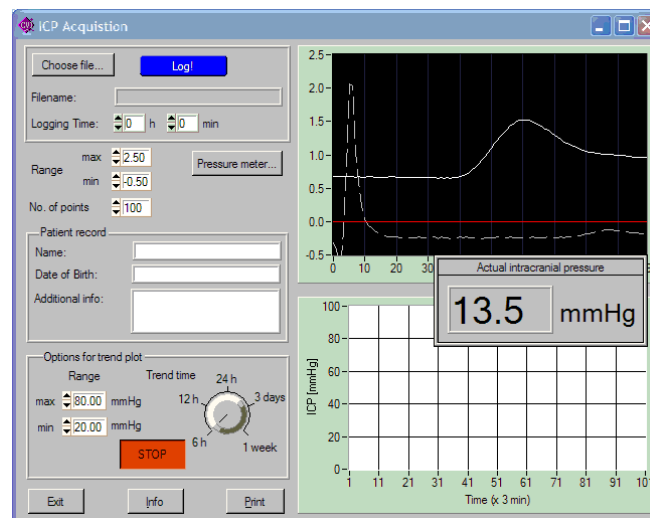
The screenshot of the data acquisition software

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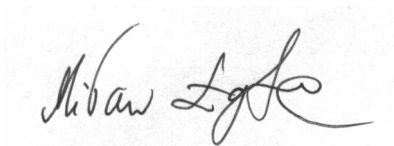
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